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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,413	12/17/2003	Ralph R. Binetti	SC66U-US	8915

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/738,413	BINETTI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 5/30/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 3/30/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-39 are pending in the instant application.

The subject matter of the claims that is not directed to the elected sequences, SEQ ID NOs: 1 and 2, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Response to Arguments--Claim Rejections - 35 USC § 112, first paragraph

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

It is noted that applicant has amended the claims to delete the term "prevent" which obviates one aspect of the enablement rejection of record. However, the rejection is maintained for the reasons explained in the office action mailed on 3/30/07 and reiterated below.

Applicant asserts that use of in vitro experiments to establish in vivo events is, in principle, a valid methodology to correlate the *in vitro* results provided and the *in vivo* effects of the claimed invention. However, the in vitro experiments need be commensurate in scope with the in vivo effects of the claimed invention. In the instant case, the specification describes a Northern Dot Blot experiment to measure tyrosinase mRNA in a B16 mouse melanoma cell line after 48-hour treatment with a tyrosinase siRNA in vitro.

Evidence of an in vitro decrease in expression of tyrosinase after treatment with a tyrosinase siRNA is not a teaching commensurate in scope with the instant methods for treating hyperpigmentation or any other unwanted pigmentation having the effect of ameliorating, reducing and/or eliminating the hyperpigmentation or other unwanted pigmentation in a subject in need of treatment. Importantly, the specification does not disclose which tyrosinase siRNA was used in the Northern Dot Blot experiment. This is important because the claims are directed to those siRNA oligomers that target mouse and human tyrosinase. Furthermore, the specification does not exemplify any topical administration of a siRNA oligomer having the desired outcome.

In the instant case, applicant has not provided a particular model that is recognized as correlating siRNA oligomers specific for mouse and human tyrosinase mRNA to the desired effect on the broad genus of conditions that are instantly recited.

Additionally, siRNA oligomers are known to face in vivo delivery challenges that do not allow for in vitro delivery to be easily applied to in vivo effects, as supported by the art relied upon by the examiner. The instant method is unpredictable in nature due to the unpredictability of siRNA delivery in vivo coupled with the lack of a working example commensurate in scope with the instant claims in the instant specification. One would have to perform undue experimentation in order to predictably practice the claimed invention.

Applicant relies upon teachings in the art that skin lightening agents, such as hydroquinone and vitamin C typically lighten the skin and thus concludes that inhibition of tyrosinase expression occurs in vivo and draws a nexus between inhibition of tyrosinase and hyperpigmentation. It is agreed that there is a nexus in the art between inhibition of tyrosinase and hyperpigmentation. However, the unpredictability of the instant method is based on the breadth of the desired outcome embraced by the instant claim language as well as the specific unpredictability of siRNA oligomer delivery in vivo absent a working example. The instant claims are directed to "ameliorate, reduce and/or eliminate" the hyperpigmentation, although applicant has shown one Northern Dot Blot with some reduced expression of one siRNA oligomer. Skin lightening agents such as hydroquinone and vitamin C do not face the same delivery challenges that siRNA oligomers and do not act via the same mechanism once in the cell.

Contrary to applicant's assertions, the instant specification does not provide a sufficient amount of guidance necessary for one of skill in the art to practice the instant method without undue experimentation, as discussed above.

Applicant asserts that the Caplen et al. reference does not address unpredictability of inhibiting tyrosinase expression via RNAi but rather addresses general unpredictability of the delivery of siRNA molecules. Applicant asserts that Caplen et al. does not call into question the predictability and outcome of the claimed invention because Caplen distinguishes RNAi over previous gene therapy approaches as an advantageous method. It is agreed that RNAi is an advantageous and preferable method in the art for downregulation of gene expression. However, as evidenced by Caplen et al, the in vivo delivery of such molecules remains to be a challenge that needs to be addressed.

Applicant asserts that Zhang et al. does not address the topical administration of siRNAs, as instantly claimed and teaches that siRNA delivery to mammalian cells will not be so simple but can be achieved. Again, it is agreed that there have been successful instances of siRNA oligomer delivery in vivo. However, in vivo delivery remains to be a major obstacle for siRNA oligomers, absent a teaching commensurate in scope with the instant claims to the contrary.

Applicant discusses the teachings of Hartmann et al. regarding the unpredictability of treating the scope of instantly recited pigmentations. Applicant argues that Hartmann et al. teach hypopigmentary disorders, rather than the hyperpigmentations that are instantly claimed. Contrary to applicant's assertions, the

instant claims are not only directed to hyperpigmentations. The claims are directed to treating hyperpigmentation "or other unwanted pigmentation" which includes any type of unwanted pigmentation, such as hypopigmentations. Hartmann et al. is evidence of the broad scope of disorders that are embraced by the instant claim language "or other unwanted pigmentation.

MPEP 2164.08 explains that the questions of enablement are evaluated against the claimed subject matter and the focus of the examination inquiry is whether **everything** within the scope of the claim is enabled. Applicant is claiming treatment effects of any unwanted pigmentation via administering any siRNA oligomer specific for mouse and human tyrosinase. The specification is not enabling for treatment, amelioration, reduction and/or elimination of such a vast genus of disorders via administering such a broad genus of siRNA oligomers.

New Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 5-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to methods of administering to the skin of a subject in need thereof a composition comprising one or more siRNA oligomers specific for mouse and human tyrosinase mRNA in an amount effective to ameliorate, reduce and/or eliminate the hyperpigmentation or other unwanted pigmentation. The invention is further directed to specific dosing and delivery requirements.

The instant claims are not directed to a method comprising topically administering one or more siRNA oligomers specific for mouse tyrosinase mRNA or human tyrosinase mRNA, but are directed to a method of utilizing only those siRNA molecules that are specific for "mouse and human" tyrosinase mRNA. The instant specification discloses three sequences that are "homologous to sequences found in both human and mouse forms of tyrosinase". It is noted that although applicant is claiming a method involving only the specific subset of siRNAs that target both mouse and human tyrosinase mRNA, the human and mouse mRNA sequences have not been defined by applicant in a way that would allow for one of ordinary skill to envision which siRNA oligomers are directed to both sequences without further knowledge of the sequences. The instant specification does not describe a structure that imparts the function of targeting mouse and human tyrosinase mRNA.

One of ordinary skill in the art could not envision the member siRNAs of the instant method that are targeted to both human and mouse tyrosinase mRNA without

knowledge of the sequences in order to define which area of the sequences are homologous and which are not. Therefore, one would not be able to recognize that the applicant was in possession of the claimed genus at the time of filing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-9, 14-25 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. (US 2004/0215006 A1).

The invention of the above claims is drawn to methods of administering to the skin of a subject in need thereof a composition comprising one or more siRNA oligomers specific for mouse and human tyrosinase mRNA in an amount effective to ameliorate, reduce and/or eliminate the hyperpigmentation or other unwanted pigmentation. The invention is further directed to specific dosing and delivery requirements.

At the outset, it is noted that Bennett et al. is considered as enabled as the instant specification. Bennett et al. is applied as teaching the instant method although the teachings of Bennett et al. regarding in vivo effects are prophetic and are not

considered enabled, consistent with the rejection of the instant claims under 35 U.S.C. 112, first paragraph, explained above.

Bennett et al. teach methods of modulating the expression of tyrosinase in cells, tissues, or animals comprising contacting said cells, tissues, or animals with one or more of the compounds or compositions of the invention. Bennett et al. teach methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of tyrosinase (see page 2, paragraph 0016, for example). Bennett et al. teach that the compounds of the invention can be single or double stranded antisense oligonucleotides (see page 3, paragraphs 0025 and 0026; and example 5).

Bennett et al. teach that the color of mammalian skin and hair is determined largely by the degree and distribution of melanin production and teach that the involvement of tyrosinase in melanoma make its selective inhibition an appropriate point for therapeutic intervention in these disorders (see page 1). Bennett et al. teach that antisense oligonucleotides pointed to tyrosinase in skin cosmetics have been used to beautify and whiten the skin and teach that antisense oligonucleotides targeting the tyrosinase gene have been used as depigmentation or skin whitening agents in a cosmetic composition or a dermatologic composition (see page 1).

Bennett et al. specifically teach that the compounds of the invention can be formulated in topical formulations and that administration may be topical. The topical formulations of Bennett et al. such as lotions and creams are taught to be administered topically and would therefore necessarily be applied to some portion of the face,

forehead, neck, arms, hands, legs, knees, feet, chest, back, groin, or buttocks, as instantly recited. Bennett et al. teach that pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional carriers may also be incorporated (see page 10). Bennett et al. teach that preferred formulations for topical administration include those in which the oligonucleotides are in admixture with a topical delivery agent such as lipids and liposomes (see page 11). The instant specification does not define "biodegradable microsphere", as recited in instant claim 26. The liposomes and delivery agents of Bennett et al. are considered to meet this instant limitation.

Bennett et al. teach various dosing parameters and teach that generally dosage is from 0.01 ug to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years (see page 12).

The instant specification does not define what is meant by "sensitive skin", as recited in instant claim 18. The subjects being treated by the method of Bennett et al. for a tyrosinase related disorder such as melanoma are considered to have sensitive skin, as instantly recited.

As explained in the written description rejection above, the instant specification does not describe a structure that imparts the function of targeting mouse and human tyrosinase mRNA. Bennett et al. specifically teach oligomers that target human or mouse tyrosinase mRNA and are therefore necessarily considered to teach oligomers that would target both.

Therefore, the instant invention is anticipated by Bennett et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 2004/0215006 A1), in view of Mahashabde et al. (US 6,436,378 B1), and Perricone (US 2002/0141956 A1).

The invention of the above claims is drawn to methods of administering to the skin of a subject in need thereof a composition comprising one or more siRNA oligomers specific for mouse and human tyrosinase mRNA in an amount effective to ameliorate, reduce and/or eliminate the hyperpigmentation or other unwanted pigmentation. The invention is further directed to specific dosing and delivery requirements.

At the outset, it is noted that Bennett et al. is considered as enabled as the instant specification. Bennett et al. is applied as teaching the instant method although the teachings of Bennett et al. regarding in vivo effects are prophetic and are not considered enabled, consistent with the rejection of the instant claims under 35 U.S.C. 112, first paragraph, explained above.

Bennett et al. teach methods of modulating the expression of tyrosinase in cells, tissues, or animals comprising contacting said cells, tissues, or animals with one or more of the compounds or compositions of the invention. Bennett et al. teach methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of tyrosinase (see page 2, paragraph 0016, for example). Bennett et al. teach that the compounds of the invention can be single or double stranded antisense oligonucleotides (see page 3, paragraphs 0025 and 0026; and example 5).

Bennett et al. teach that the color of mammalian skin and hair is determined largely by the degree and distribution of melanin production and teach that the involvement of tyrosinase in melanoma make its selective inhibition an appropriate point for therapeutic intervention in these disorders (see page 1). Bennett et al. teach that antisense oligonucleotides pointed to tyrosinase in skin cosmetics have been used to beautify and whiten the skin and teach that antisense oligonucleotides targeting the tyrosinase gene have been used as depigmentation or skin whitening agents in a cosmetic composition or a dermatologic composition (see page 1).

Bennett et al. specifically teach that the compounds of the invention can be formulated in topical formulations and that administration may be topical. The topical formulations of Bennett et al. such as lotions and creams are taught to be administered topically and would therefore necessarily be applied to some portion of the face, forehead, neck, arms, hands, legs, knees, feet, chest, back, groin, or buttocks, as instantly recited. Bennett et al. teach that pharmaceutical compositions and

formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional carriers may also be incorporated (see page 10). Bennett et al. teach that preferred formulations for topical administration include those in which the oligonucleotides are in admixture with a topical delivery agent such as lipids and liposomes (see page 11). The instant specification does not define "biodegradable microsphere", as recited in instant claim 26. The liposomes and delivery agents of Bennett et al. are considered to meet this instant limitation.

Bennett et al. teach various dosing parameters and teach that generally dosage is from 0.01 ug to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years (see page 12).

The instant specification does not define what is meant by "sensitive skin", as recited in instant claim 18. The subjects being treated by the method of Bennett et al. for a tyrosinase related disorder such as melanoma are considered to have sensitive skin, as instantly recited.

As explained in the written description rejection above, the instant specification does not describe a structure that imparts the function of targeting mouse and human tyrosinase mRNA. Bennett et al. specifically teach oligomers that target human or mouse tyrosinase mRNA and are therefore necessarily considered to teach oligomers that would target both.

Bennett et al. does not teach for the composition to comprise a sunscreen, such as octylmethoxycinnamate, and does not teach alpha hydroxy acid.

Mahashabde et al. teach a composition comprising a cream or lotion base said base further comprising a) an active agent or mixture thereof which brings about skin lightening, and b) an active agent or mixture thereof which prevents skin from further darkening when exposed to ultraviolet light (see abstract and claim 1). Mahashabde et al. teach that the agent to lighten skin can be those which can inhibit the synthesis of melanin such as tyrosinase inhibitors and that the agent to prevent further darkening when exposed to UV light can be a sunscreen such as octylmethoxycinnamate (OMC) (see column 1).

Perricone teaches a method for whitening skin comprising topically administering to the skin a composition comprising alpha hydroxy acid (see claims 1 and 7). Perricone teaches that some embodiments of the skin whitening composition contain adjunct ingredients that enhance the efficacy and stability of skin whitening formulations such as a tetronic acid derivative that inhibits tyrosinase (see abstract).

It would have been obvious to incorporate a sunscreen, such as octylmethoxycinnamate, as taught by Mahashabde et al. or alpha hydroxy acid, as taught by Perricone, into the composition of the method of Bennett et al.

One would have been motivated to incorporate a sunscreen, such as octylmethoxycinnamate, as taught by Mahashabde et al. or alpha hydroxy acid, as taught by Perricone, into the composition of the method of Bennett et al. because Bennett et al. teach a method of topically administering a composition comprising one or more siRNA molecules (double stranded oligonucleotides) targeted to tyrosinase mRNA to modulate the expression of tyrosinase in cells and thereby treat a human in need

thereof. Therefore, one would have been motivated to optimize the method by incorporating other agents that were known in the art to achieve the same benefit of treating a tyrosinase disorder or lightening skin pigmentation.

Since Mahashabde et al. teach a composition comprising a) an active agent or mixture thereof which brings about skin lightening, such as a tyrosinase inhibitor and b) an active agent or mixture thereof which prevents skin from further darkening when exposed to ultraviolet light, such as octylmethoxycinnamate (OMC), one would have been motivated to combine OMC with the tyrosinase inhibitor of Bennett et al. to achieve the same benefit.

Furthermore, one would have been motivated to incorporate alpha hydroxy acid into the composition of the method of Bennett et al. because Perricone teaches a method for whitening skin comprising topically administering to the skin a composition comprising alpha hydroxy acid. Perricone teaches that some embodiments of the skin whitening composition contain adjunct ingredients that enhance the efficacy and stability of skin whitening formulations such as a tetronic acid derivative that inhibits tyrosinase (see abstract).

Therefore, both Mahashabde et al. and Perricone teach beneficial ingredients for compositions that lighten skin pigmentation and each teach that these compositions can also comprise tyrosinase inhibitors. Therefore, one would have a reasonable expectation of success given that Bennett et al. teaches a method comprising administering a topical siRNA directed to tyrosinase that the ingredients of Mahashabde et al. and Perricone would further optimize the outcome of the method of Bennett et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

AHB

/J. E. Angell/
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